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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,695	11/20/2001	Gabriel Lopez-Berestein	UTSC:648US	9730

7590 07/14/2004

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,695	LOPEZ-BERESTEIN ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 4-19-04 is acknowledged.

Claims included in the prosecution are 1-2 and 4-32.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 2 now recites micelles comprising phospholipids. A careful review of the specification (see page 30 of the specification in particular) indicates that there is no support for this amended claim and therefore, deemed to be new matter.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Weiner et al similarly teach the advantages of using liposomes as carriers of drugs and their sustained release and site-specific release of drugs (note Introduction and page 1553).

The use of liposomes as carriers for imexon would have been obvious to one of ordinary skill in the art because of the advantages of liposomes taught by Sugarman, Ranade, Mayer et al and Weiner et al. The criticality of the use of phosphatidylcholine and phosphatidylglycerol with a specific fatty acid chain such as myristic acid is not readily apparent in the absence of unexpected results since these are commonly used phospholipids in the preparation of liposomes as also evident from Sugarman. The use of derivatives of imexon would have been obvious to one of ordinary skill in the art since active skeleton is the cyanoaziridine structures and therefore, one would expect at least similar results obtained using imexon.

Note: claim 2 is included in the rejection since liposomes are also called micelles as noted from Presant (5,435,989), which is cited of interest.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that one of the elements that is required for a prima facie case of obviousness to exist is that there must be some suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings of Hermann in view of either Sugarman, Ranade, Mayer, and Weiner and that none of the references make any suggestion of delivering imexon via administration of liposomes. These arguments are not found to be persuasive. As recognized by applicant himself there should be a

motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings. In instant case there is a clear motivation in the secondary references for one of ordinary skill in the art to use liposomes for the delivery of imexon. Sugarman, and Ranade in particular teach the advantages of using liposomes as sustained delivery agents for both hydrophobic and hydrophilic active agents, cancer agents in particular and that of Mayer shows the increased uptake of the liposomes containing an anti-cancer drug by the tumor cells. Furthermore, liposomal art is well advanced in the sustained delivery of a variety of drugs and therefore, motivation to use liposomes comes from the knowledge available to one of ordinary skill in the art. Applicant argues that none of the drugs mentioned in the references have any similarity or structural resemblance to imexon and that hundreds of drugs exist for treating cancer such that one skilled in the art could not possibly know that imexon would be a drug appropriate for liposome delivery. This argument is not found to be persuasive since the novelty is the sustained delivery nature of the liposomes themselves and this sustained delivery does not depend upon the drug encapsulated and therefore, one of ordinary skill in the art would expect at least the same results using imexon as the drug. It is interesting to note that instant claim 1 recites just 'phospholipids' and includes even imexon derivatives. Based on applicant's own logic, just because liposomes are effective in the delivery of imexon, one cannot predict the same nature of the results with any imexon derivative (see claim 24 which recites several imexon derivatives) and phospholipids in a 'non-liposomal form'. It is the examiner's position that prima facie case of obviousness has been

established. Instant specification contains no data at all to show the effectiveness of the liposomal imexon, let alone various derivatives of imexon claimed.

5. Claims 1-2 and 4-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/00120, further in view of either of the references of Sugarman et al (Critical Reviews in Oncology Hematology, 1992 or Ranade (J. Clin Pharmacol., 1989 or Mayer et al (Cancer Letters, 1990) or Weiner et al (Drug development and Industrial Pharmacy, 1989).

WO discloses imexon and several of the claimed derivatives for treating cancer (abstract, pages 3-5). WO also teaches the use of imexon in combination with other anti-cancer agents (page 25). What is lacking in WO is the teaching of the use of liposomes as carriers for the delivery of imexon or its derivatives for the treatment of cancer or stimulating the immune system. It should be noted however that WO teaches the use of slow release carriers on page 22.

As pointed out above, Sugarman while reviewing the use of liposomes as carriers of drugs in the treatment of malignancy teaches that liposomes are sustained release agents and the advantages of their use as carriers of drugs include reduced toxicity associated with those drugs. Sugarman also teaches the use of DMPC/DMPG in a ratio of 7:3. Sugarman further teaches that attachment of monoclonal antibodies to the surface of liposomes to direct the liposomes to the target tissue is known in the art (see entire publication, Introduction and Rationale and Table 1 in particular).

Ranade similarly discloses the advantages of using liposomes as carriers of drugs and their sustained release and site-specific release of drugs (pages 685

691).

Mayer et al teach the tumor uptake and anti-tumor efficacy of doxorubicin against murine mammary tumors (note the summary).

Weiner et al similarly teach the advantages of using liposomes as carriers of drugs and their sustained release and site-specific release of drugs (note Introduction and page 1553).

The use of liposomes as carriers for imexon or its derivatives taught by WO would have been obvious to one of ordinary skill in the art because of the advantages of liposomes taught by Sugarman, Ranade, Mayer et al, and Weiner et al. The criticality of the use of phosphatidylcholine and phosphatidylglycerol with a specific fatty acid chain such as myristic acid is not readily apparent in the absence of unexpected results since these are commonly used phospholipids in the preparation of liposomes as also evident from Sugarman.

Note: claim 2 is included in the rejection since liposomes are also called micelles as noted from Presant (5,435,989), which is cited of interest.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments are similar to those raised for the above 103 rejection and therefore, the same response is deemed applicable.

6. Claims 1-2 and 4-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hermann or WO cited above, in view of Presant (5,435,989).

The teachings of Hermann and WO have been discusses above. What is lacking in these references is the teaching of the use of phospholipid micelles or liposomes.

Presant teaches that when micellar particles such as liposomes containing active agents are injected into the host, there is an enhanced retention of the active agent in the tumor cells (abstract, col. 3, line 13 through col. 9, line 21 and claims).
The use of micellar particles such as liposomes for the delivery of imexon taught by Hermann or WO would have been obvious to one of ordinary skill in the art since Presant shows enhanced accumulation of these particles at the tumor site. The criticality of the use of phosphatidylcholine and phosphatidylglycerol with a specific fatty acid chain such as myristic acid in specific ratios is not readily apparent in the absence of unexpected results since these are commonly used phospholipids in the preparation of liposomes. The specification shows no data to indicate the criticality. As pointed out above, the use of derivatives of imexon would have been obvious to one of ordinary skill in the art since active skeleton is the cyanoaziridine structures and therefore, one would expect at least similar results obtained using imexon.

3. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

G S Kishore

Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK